REMARKS/ARGUMENTS

I. Status of the claims

Claims 1-66 are pending. Claims 41-50 have been withdrawn from consideration as drawn to a non-elected invention.

II. The Amendments Herein

No new matter has been added by the present amendments.

Claims 1, 27, 33, 51, 60 and 64 have been amended herein to recite that the claimed polypeptides have both an antibody heavy chain variable region and an antibody light chain variable region. The amendment is supported throughout the specification, including Figure 1. These claims have also been amended to clarify that the affinity of the polypeptides for the antigen is 5 times that of the parental antibody for the same antigen, as supported throughout the specification, including page 22, lines 31-33. The word "mutant" has been deleted from these claims as unnecessary since the variation of the sequence of the claimed polypeptides from that of the parental antibody is specified by elements (a) and (b) of these claims.

Claims 2-5, 52, and 53 have been amended to accord with the changes in the claims from which they depend.

Claim 21 has been amended to recite that the scFv is expressed in conjunction with gIIIp surface protein of a filamentous bacteriophage. The amendment is supported by, e.g., page 29, lines 3-5.

III. The Office Action

Applicants note with appreciation that the current Action withdraws a number of grounds of rejection made in the previous Office Action.

The current Action rejects claims 1-40 and 51-66 on a variety of grounds. Applicants amend in part and traverse all the rejections. The rejections are discussed separately below in the order in which they appear in the Action.

A. Rejections Under 35 U.S.C. § 112, First Paragraph

1. Rejection of Claims Because there is No Sequence Information for Constant and Hinge Regions

The Action rejects claims 6, 7, 11, 17-20, 22,-26, 35 and 51-62 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable the person of skill to practice the invention. According to the Action, the claims are drawn to the complete SS antibody and not just the variable heavy and light chains. The Action states that Figure 1 does not provide any information about the CH1, CH2, CH3, or hinge regions of the antibody, and therefore the practitioner does not have all the information necessary to make and use the invention commensurate in scope with the claims. Action, at pages 4-5. Applicants traverse.

The rejection appears premised on the belief that the SS antibody is a complete immunoglobulin molecule and that the Applicants have not enabled it because they have not set forth the complete native sequence of the antibody. SS was, however, developed as a single chain Fv through phase display; it was not never a complete immunoglobulin molecule with constant regions and hinge regions. See, specification at page 10, lines 13-17. Thus, the scFv sequence set forth in Figure 1 is the complete SS sequence.

The Action correctly notes that the claims read on intact antibodies as well as antibody fragments that retain antigen recognition (for convenience of reference, all these antibody forms are encompassed within the term antibody, as used in the present specification. See, page 12, lines 14-24. This is common in antibody applications, as evidenced by Marks, U.S. Patent No. 5,977,322, cited by the previous Action *against* the claims, at column 4, lines 46-54). It is also known in the art that it is the complementarity determining regions (CDRs) of the variable region of the antibody that form the antigen binding site, and which therefore confer antigen specificity. Jones et al. demonstrated this dramatically in 1986 by substituting the CDRs of a human myeloma protein with CDRs from a mouse antibody and showing that the new chimeric antibody had the antigen specificity of the mouse antibody from which the CDRs originated. See, e.g., Jones et al., Nature, 321:522-5 (1986) (abstract enclosed).

The constant and hinge regions, by contrast, are involved in activating complement activity, but not in antigen recognition. This fact has been exploited in the art, since

before the priority date of the application, by developing antibodies in mice and then replacing the constant and hinge regions of the murine antibodies with human sequences to reduce immunogenicity when the chimeric construct is introduced into humans. Rituxan® ("Rituxumab"), for example, is an anti-CD20 chimeric antibody against B cell non-Hodgkin's lymphoma. The antibody was approved for human use in 1997, well before the priority date of the subject application (see attached pages on "Rituxan timeline"). The antibody is comprised of "murine light- and heavy-chain variable region sequences and human constant region sequences." See, page 1 of Rituxan® product prescribing information. At page 2, the prescribing information explains: "The Fab domain of Rituximab [which, as noted, is the murine variable region] binds to the CD20 antigen on B lymphocytes, and the Fc domain [which, as noted, is part of the human constant region sequences] recruits effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of action of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell mediated cytotoxicity (ADCC)." For the Examiner's convenience, pages 1 and 2 of the prescribing information are enclosed. *See also*, Huston and George, Hum. Antibodies 10(3-4):127-42 (2001) (abstract enclosed).

Applicants respectfully remind the Examiner that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.". MPEP § 2164.01, *quoting, United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). As shown by Jones et al., it was known for more than a decade before the priority date of the subject application that antigen recognition could be altered by substituting CDRs; and the approval of Rituxan® in 1997 shows that, before the priority date of the subject application, persons of skill could take the variable regions of an antibody and human constant regions and combine the two to create chimeric antibodies. Thus, persons of skill needed only the sequence of the SS variable regions provided by the present specification to make full immunoglobulin molecules that had the antigen specificity and affinity of the SS antibody. The Action sets forth no reason why, for example, the human constant regions used for Rituxan® could not be used in combination with the SS variable regions to construct a complete immunoglobulin molecule.

Applicants respectfully maintain that, in the words of the Court cited by MPEP 2164.01, "one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." The application sets forth sequence information sufficient to permit practitioners to make and use the invention in combination with information known in the art. Reconsideration and withdrawal of the rejection are respectfully requested.

B. Rejection of claims 1-7, 12-40, 51-55, and 57-66

The Action rejects claims 1-7, 12-40, 51-55, and 57-66 under §112, first paragraph as not enabled. The Action contends that the specification does not enable polypeptides having only an antibody heavy chain variable region or an antibody light chain variable region or a nucleic acid encoding such a polypeptide and having 5 times the affinity of a parental antibody. The Action acknowledges that Kuan and Pastan, Proc Natl Acad Sci USA 93:974-978 (1996), provided by the Applicants, shows that an immunotoxin comprising only a VH domain could successfully target immunoconjugates to target cells, but states that the reference does not show that the artisan could produce a mutated heavy chain that binds antigen with at least 5 times the affinity of the parental antibody. The Action argues that "while it appears that Kuan and Pastan teach a single chain immunotoxin that binds antigen albeit with reduced affinity, this is the exception and not the norm in the antibody art." Action, at pages 6-7. Applicants amend in part and traverse.

For the sake of good order, Applicants respectfully point out that it has been known since the early 1990's that there are naturally occurring antibodies that lack the light chain. It was discovered in 1993 that camel antibodies lack light chains. See, e.g., Hamers-Casterman et al., Nature 363:446-448 (1993) (abstract enclosed), and this was later found to be true for llamas as well (llamas and camels are collectively known as "camelids"), and these heavy-chain variable domain antibodies were found to have high affinity for protein antigens. See, e.g., Spinelli et al., Biochemistry, 39(6):1217-22 (2000) (abstract enclosed). Presumably, not all of these antibodies are of equal affinity, and the Action's thesis that single chain antibodies cannot show affinity 5 times greater than a parental antibody is incorrect. The

Action's position is therefore further contradicted by the fact that an entire group of animals have functional, high affinity antibodies that do not comprise light chains at all.

To expedite prosecution, however, the claims have been amended to recite that the claimed polypeptides have both an antibody variable heavy chain and an antibody variable light chain. Reconsideration and withdrawal of the rejection are respectfully requested.

C. Rejection under 35 U.S.C. § 103(a) over Chowdhury (a) in view of Wagner and Pastan

Claims 1-6, 8-21, 27, 28, 31-34, 36, 37, 39, 40, 51-54, 56-61, 63, 64, and 66 are rejected under 35 U.S.C. § 103(a) as anticipated by Chowdhury et al., Proc Natl Acad Sci USA 95:669-674 (1998) ("Chowdhury (a)") in view of Wagner et al., Nature 376:732 (1995) ("Wagner"), Pastan et al., U.S. Patent No. 6,083,502 ("Pastan"), and Adams et al., Cancer Research 58:485-490 (1998) ("Adams"). The Action, at pages 7-8. The Action indicates that the "combination of references relied upon was not based on the mutation of hot spot motifs following affinity selection by phage display." Action, at page 8. Rather, the Action reiterates that Chowdhury (a) was cited because it teaches the high affinity SS antibody and Wagner was cited because it teaches the hot spot motifs are preferred targets for mutation. The Action then reiterates the allegation that the skilled artisan would have "been motivated to only mutate CDR hot spots in the SS antibody in order to increase the affinity of the SS antibody without screening large and multiple antibody phage libraries, avoid deleterious mutations in the structural scaffold of the antibody." Action, at page 9. Applicants traverse.

Applicants respectfully observe that they did not intend to suggest that the rejection in the previous Action was based on combining the references to find the mutation of hot spot motifs following affinity selection by phage display. What Applicants did intend was to point out (1) that the SS antibody taught by Chowdhury (a) was already a high affinity antibody which had been selected for by multiple rounds of phage display, (2) that Wagner's teaching regard the normal maturation of antibody affinity, and (3) that Wagner contains no teaching or suggestion that antibodies which have been selected for high affinity through the artificial process of phage display can undergo further increases in affinity through mutations in CDR

hotspots. Therefore, Applicants maintained that the person of skill would be likely to conclude that the antibodies selected by the phage display process, and displaying the affinity reported in Chowdhury (a) had already undergone mutation at these hot spots and obtained whatever benefit was available from such mutations. Applicants further observe that Wagner contains no teaching or suggestion that the process of affinity maturation it describes for natural antibodies would permit generation of antibodies with 5 times the affinity of a parental antibody, and therefore does not teach or suggest all of the recitations of the claims under examination.

Adams does not make up this deficiency since it is only cited to indicate that higher affinity antibodies are generally desirable as targeting agents. In short, Applicants maintain that the combination of references made by the Action do not teach or suggest the invention as claimed.

Applicants respectfully request reconsideration and withdrawal of the rejection.

D. Rejection of the Claims As Indefinite

Claims 1-21, 27-29, and 33-40 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Action asks if the polypeptide comprising the mutated regions bind the antigen bound by the parental antibody or bind the antigen with at least five times higher affinity relative to the parental antibody's affinity for the antigen.

The amendments to the claims address the Action's concern. Reconsideration and withdrawal of the rejection is respectfully requested.

E. Rejection of Claim 21 as Not Complying with Written Description Requirement

Claim 21 is rejected under 35 U.S.C. § 112, first paragraph as not complying with the written description requirement. According to the Action, the amendment to claim 21 made in the Applicants' previous response added new matter by introducing the language "expressed in conjunction with a surface protein of a bacteriophage." The Action maintains that the specification only discloses scFvs expressed in conjunction with gIIIp of filamentous phage.

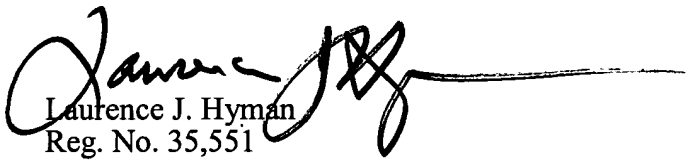
Claim 21 has been amended to recite that the scFv is expressed in conjunction with gIIIp surface protein of a filamentous bacteriophage. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, he is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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